*Case Report*
*J Vet Intern Med* 2011;25:1454–1457

# Renal Tubular Acidosis Associated with Zonisamide Therapy in a Dog

A.K. Cook, A.K. Allen, D. Espinosa, and J. Barr

A 5-year-old neutered male Schipperke was evaluated by the internal medicine service at Texas A&M College of Veterinary Medicine and Biomedical Sciences for mild increases in blood urea nitrogen (BUN) and creatinine concentrations. Parameters on an automated complete blood count[a] performed at the same time were within the reference ranges. The dog had a 3-year history of epileptiform seizures, which had been successfully managed for 18 months with oral zonisamide (ZNS) at a dosage of 7.9–8.4 mg/kg every 12 hours. Peak serum ZNS concentration had been measured 1 year earlier, and was within the target range at 39 μg/mL.

On presentation to the internal medicine service, the dog was alert and responsive. Physical examination was essentially unremarkable, although the dog panted persistently and appeared agitated. A serum chemistry panel was performed[b] ; notable laboratory findings included hyperchloremia (124 mmol/L; normal: 107–116 mol/L), hypernatremia (150 mmol/L; normal: 139–147 mmol/L), hypokalemia (3.1 mmol/L; normal: 3.3–4.6 mmol/L), hypophosphatemia (1.6 mg/dL; normal: 2.9–6.2 mg/dL), and low total carbon dioxide ($TCO_2$; 11 mmol/L, reference range: 21–28 mmol/L). BUN and creatinine were 25 mg/dL (normal: 5–29 mg/dL) and 1.5 mg/dL (normal: 0.3–2.0 mg/dL), respectively. Urine, collected via cystocentesis, was adequately concentrated with a specific gravity of 1.039[c] and a urine pH of 6.5 based on dipstick assessment.[d] Trace proteinuria was confirmed with a sulfosalicylic acid test. Urine protein:creatinine ratio was < 0.02 (< 0.5 considered normal). Urine culture produced a single colony of a *Micrococcus* species on the 1 : 1,000 dilution plate; this was assumed to be a contaminant. Ultrasonographic examination of the abdomen indicated hyperechogenicity of the inner part of each renal cortex; renal size was within normal limits bilaterally. The rest of the abdominal contents was unremarkable. Systolic blood pressure was measured indirectly using a Doppler device[e] and was within the reference range at 115–120 mmHg. Six hours after dosing, serum ZNS concentration was 38 μg/dL (target range: 10–40 μg/dL).

**Abbreviations:**

| | |
|---|---|
| BUN | blood urea nitrogen |
| CA | carbonic anhydrase |
| FDA | Food and Drug Administration |
| RTA | renal tubular acidosis |
| $TCO_2$ | enzymatic carbon dioxide |
| ZNS | zonisamide |

The metabolic disturbance was characterized as a hyperchloremic, normal anion gap metabolic acidosis with a low sodium-chloride difference of 5.5 (normal: 27.1–32.2), normal total plasma concentration of nonvolatile weak buffers (Atot), and normal strong ion gap.[1,2,3] The Na-Cl difference was calculated using the simplified Fencl-Stewart approach, with the Na-Cl difference defined as the sum of the delta free water (0.25 × [Na patient – Na normal] and delta chloride (Cl normal – Cl corrected), where Cl corrected = (normal/patient Na) × measured Cl. Differential diagnoses for this finding included gastrointestinal bicarbonate loss through diarrhea, renal tubular acidosis (RTA), dilutional acidosis, and administration of carbonic anhydrase (CA) inhibitors, ammonium chloride, or cationic amino acids.[1] Based on this dog's history, RTA seemed the most likely explanation. Dogs with RTA have compromised reclamation of bicarbonate from the glomerular filtrate with subsequent excessive urinary loss of bicarbonate (proximal RTA) or compromised secretion of hydrogen ions into the filtrate (distal RTA), in the presence of a normal glomerular filtration rate.[4] Both disorders can be present concurrently in the same individual or may be combined with other renal tubular reabsorptive defects. Classically, dogs with proximal RTA have an acid urine (pH < 6.0) in the presence of a hyperchloremic metabolic acidosis. Distal RTA (also referred to as classic or Type 1) is characterized by a urine pH > 6.0 in the presence of a metabolic acidosis. As this dog's urine pH was 6.5, the tentative diagnosis was distal RTA.

The dog returned to the clinic 4 days later for additional diagnostics. Arterial blood gas analysis[f] revealed a blood pH of 7.42, with a partial pressure of carbon dioxide ($PaCO_2$) of 17.8 mmHg and a bicarbonate concentration of 11.6 mmol/L. The borderline alkalemia was unexpected; although a drop in $PaCO_2$ is the anticipated compensatory response to a metabolic acidosis, the dog should not overcompensate to the point

*From the Department of Small Animal Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX 77843. Dr Allen's present address is 19779 Forest Branch Lane, Richards, TX 77873; and Dr Espinosa is presently affiliated with Cornell University Hospital for Animals, College of Veterinary Medicine, Cornell University, Ithaca, NY.*

*Corresponding author: A.K. Cook, Department of Small Animal Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX 77843; e-mail: akcook@cvm.tamu.edu*

*Submitted March 15, 2011; Revised July 27, 2011; Accepted August 15, 2011.*



*10.1111/j.1939-1676.2011.00801.x*

of inducing an alkalotic state. This dog's expected respiratory compensation for the metabolic acidosis would be a decrease in $PaCO_2$ to 31.2 mmHg (based on an anticipated 0.7 mmHg decrease in $PaCO_2$ from the normal value of 40.2 mmHg for every 1 mEq/L decrease in bicarbonate from the midpoint of the reference range).[5,6] The arterial blood gas results therefore indicated a primary respiratory alkalosis. The cause of the primary respiratory alkalosis remains unclear. It might have reflected transient hyperventilation because of anxiety, or a more chronic state because of unrecognized pulmonary disease or a centrally mediated process causing persistent hyperventilation.

Proximal and distal RTA can be differentiated by assessing the response to ammonium chloride ($NH_4Cl$) challenge or bicarbonate loading. In normal dogs, oral administration of $NH_4Cl$ results in rapid and profound acidification of the urine. A baseline urine pH was measured and 200 mg/kg of $NH_4Cl$ was administered per os. Urine samples were collected via catheterization every hour and pH was measured using a benchtop meter.[g] Urine pH was 6.7 before the start of the $NH_4Cl$ challenge and slowly decreased to a nadir of 5.50 after 6 hours. In 1 study using normal dogs, minimum urine pH was 5.16 within 4 hours of administration of $NH_4Cl$, and failure to decrease urine pH below 5.5 indicates distal RTA.[7] However, an earlier study reported a mean urine pH of 5.74 in normal dogs 5 hours after $NH_4Cl$ challenge, and suggested that failure to decrease urine pH below 6 supported a diagnosis of distal RTA whereas a pH below 5.5 would indicate proximal RTA.[8] On balance, this dog's response to acid challenge was therefore somewhat inconclusive. Current definitions of RTA in human patients are based on urinary ammonium ($NH_4^+$) excretion rather than urine pH.[9] This approach has not been described in the dog, but measuring $NH_4^+$ excretion may have provided additional information in this case and would have posed less risk than acid loading a dog with a complex acid-base disorder.

As proximal RTA can be associated with other renal tubular reabsorptive disorders, urine was tested for the presence of other unabsorbed solutes.[h] This sample was negative for marked amino aciduria, lactic aciduria, and glucosuria and was therefore not consistent with a global renal tubular disorder such as Fanconi syndrome.

Based on these findings, a diagnosis of a mixed acid-base disorder was established, characterized by a distal or mixed RTA causing metabolic acidosis and hyperventilation resulting in respiratory alkalosis. As these changes were potentially associated with ZNS administration, the dog was started on an alternative anticonvulsant.

Levetiracetam was prescribed at 20 mg/kg PO every 8 hours for seizure control. The client was instructed to decrease the ZNS dose by 18 mg (approximately 25% of original dose) every 5 days, with complete discontinuation within 3 weeks. In addition, potassium citrate was prescribed at a dose of 155 mg/kg PO twice daily to address the hypokalemia and mitigate the metabolic acidosis. This agent is routinely used in dogs with distal RTA and hypokalemia to improve serum potassium concentrations and mitigate metabolic acidosis, but could in fact have been an inappropriate choice in an alkalemic patient. However, the owner had difficulty administering the potassium citrate and discontinued this medication after only 2 doses.

The dog was reevaluated after 14 days. The client reported an improvement in the dog's anxiety levels with reduced pacing and panting in the home environment. Physical examination was unchanged, and the dog appeared less anxious while in the clinic. A complete blood chemistry and urine analysis were performed. The hyperchloremia had resolved (serum chloride 116 mmol/L); $TCO_2$ was improved but still below normal at 18 mmol/L. Serum sodium, potassium, and phosphorus concentrations were 146 mmol/L, 3.5 mmol/L and 3.4 mg/dL, respectively. Creatinine and BUN were essentially unchanged (23 mg/dL and 1.4 mg/dL, respectively). Urine pH was 8.0 (dipstick measurement), with a specific gravity of 1.042. Urine culture was negative at this time. The dog was maintained on levetiracetam at 20 mg/kg three times daily and continued to do well. A subsequent recheck examination 3 weeks later revealed $TCO_2$ (22 mmol/L), serum sodium (145 mmol/L), potassium (3.7 mmol/L), and chloride (115 mmol/L) concentrations in the reference range. On this visit, the urine pH was 7.0 (dipstick measurement) with a specific gravity of 1.043. The dog became distressed during attempts at arterial sampling, so a blood gas analysis was not performed.

ZNS (1,2-benzisoxaloe-3-methanesulfonamide) is biochemically similar to serotonin and was developed many years ago as an anticonvulsant agent.[10] The mechanism of action is not fully understood but might involve blockage of T-type calcium and voltage-gated sodium channels in the brain, along with potentiation of γ-amino butyric acid.[11–13] The drug has a sulfonamide side chain with similarity to acetozolamide which results in a weak inhibitory effect on CA.[14,15] In 2000, ZNS was approved by the US Food and Drug Administration (FDA) for the treatment of epilepsy in adult human patients and has been used off-label for other conditions including bipolar depression and migraines.[16,17]

In February 2009, the FDA issued a warning that ZNS can cause metabolic acidosis in humans and recommended routine monitoring of serum bicarbonate levels even in asymptomatic individuals.[18] In a recent report, a child on ZNS therapy was diagnosed with distal RTA and hypokalemia; this resolved when the drug was discontinued.[19] Although the mechanism behind the metabolic acidosis was not determined, it was suggested that inhibition of CA played a role. CA is a metalloenzyme that catalyzes the conversion of water and carbon dioxide into bicarbonate and hydrogen ions.[20] Various isoforms of the enzyme have been described in mammals, with the different types found in specific cellular sites. Appropriate CA activity is necessary for the reclamation of bicarbonate ions and the excretion of protons by the renal tubular epithelial

cells. In the absence of CA, this reaction proceeds slowly and is not adequate to meet metabolic demands.

Persistent untreated distal RTA can cause substantial morbidity. Nephrolithiasis (with calcium-containing stones), nephrocalcinosis (attributable to decreased urinary citrate concentration), bone demineralization (caused by loss of bone buffer stores), and urinary potassium wasting all occur in human patients with this disorder.[4,21] There are numerous mechanisms behind the development of RTA; inhibition of CA was hypothesized in this dog, but compromise to various hydrogen transporters or mistargeting of the chloride/bicarbonate anion exchanger has been described in humans.[4,22]

The most commonly reported adverse effects in humans administered ZNS include drowsiness, loss of appetite, dizziness, headache, nausea, agitation/irritability, and hypohidrosis (Zonegran® [zonisamide] package insert). Although more severe problems are less common, ZNS has been associated with psychosis in up to 18% of human patients, manifest by auditory and visual hallucinations, severe depression, and episodes of paranoia.[23]

The owner of the dog described in this report noted that the dog appeared anxious with panting and restlessness while on ZNS. Some degree of hyperventilation would be expected in a dog with a metabolic acidosis, but it is possible that the drug induced some form of psychosis that worsened the hyperventilation and caused the primary respiratory alkalosis. The panting and anxiety resolved when the ZNS was discontinued and the dog was reported to be more comfortable in the home.

Although ZNS is not FDA approved for use in dogs, it is now widely used as an anticonvulsant in this species.[24] Limited information is available regarding safety, but small studies have suggested that routine clinical laboratory tests are unchanged with prolonged use, although serum thyroxine concentrations can be suppressed and mild hepatic changes might occur with sustained high doses (75mg/kg/day; approximately 5 times standard therapeutic doses).[25]

As the acid-base changes began after initiation of ZNS and resolved when the drug was discontinued, it seems likely that the ZNS played a role in this patient's disorder. On the basis of these findings, routine surveillance of serum electrolytes and acid-base status may be warranted in patients receiving ZNS. An increase in serum chloride concentration and a decrease in $TCO_2$ should prompt further investigation or a change in medication.

## Footnotes

[a] Cell-Dyn 3700; Abbott Laboratories, Abbott Park, IL
[b] Vitros 250; Ortho-Clinical Diagnostics, Rochester, NY
[c] Hand-held refractometer; General Tools, New York, NY
[d] Multistix 10SG; Seimens, Washington, DC
[e] Parks Medical Electronics, Las Vegas, NV
[f] Critical Care Xpress, Nova Biomedical Corporation, Waltham, MA
[g] Orion 3 star pH benchtop; Thermo Electron Corporation, Marietta, OH
[h] Fanconi syndrome urine metabolic test; Metabolic Genetic Screening Laboratory, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA

## References

1. DiBartola SP. Metabolic acid-base disorders. In: DiBartola SP, ed. Fluid, Electrolyte and Acid-Base Disorders in Small Animal Practice. 3rd ed. Philadelphia, PA: Saunders; 2006:250–321.

2. de Morais HA, Constable PD. Strong ion approach to acid-base disorders. In: DiBartola SP, ed. Fluid, Electrolyte and Acid-Base Disorders in Small Animal Practice, 3rd ed. Philadelphia, PA: Saunders; 2006:310–321.

3. Leisewitz AL, Jacobson LS, de Morais HS, Reyers F. The mixed acid-base disturbances of severe canine Babesiosis. J Vet Intern Med 2001;15:445–452.

4. Soriano JR. Renal tubular acidosis; the clinical entity. J Am Soc Nephrol 2002;13:2160–2170.

5. de Morais HA, Leisewitz AL. Mixed acid-base disorders. In: DeBartola SP, ed. Fluid, Electrolyte and Acid-Base Disorders in Small Animal Practice, 3rd ed. Philadelphia, PA: Saunders; 2006:296–309.

6. Haskins S, Pascoe PJ, Ilkiw JE, et al. Reference cardiopulmonary values in normal dogs. Comp Med 2005;55:156–161.

7. Shaw DH. Acute response of urine pH following ammonium chloride administration in dogs. Am J Vet Res 1989;50:1829–1830.

8. Polzin DJ, Osborne AC, Ford WB. Canine distal renal tubular acidosis in urolithiasis. Vet Clin North Am Small Anim Pract 1986;16:241–250.

9. Carlisle EJF, Donnelly SM, Halperin ML. Renal tubular acidosis (RTA): Recognize the ammonium defect and pHorget the urine pH. Pediatr Nephrol 1991;5:242–248.

10. Leppik IE, Willmore LJ, Homan RW, et al. Efficacy and safety of zonisamide: Results of a multicenter study. Epilepsy Res 1993;14:165–173.

11. Peters DH, Sorkin EM. Zonisamide: A review of its pharmacologic and pharmacokinetic properties, and therapeutic potential in epilepsy. Drugs 1993;45:760–787.

12. Suzuki A, Kawakami K, Nishimura S, et al. Zonisamide blocks T-type calcium channel in cultured neurons of rat cerebral cortex. Epilepsy Res 1992;12:21–27.

13. Kito M, Maeharat M, Watanabe K. Mechanisms of T-type calcium channel blockade by zonisamide. Seizure 1996;5:115–119.

14. Masuda Y, Karasawa T. Inhibitory effect of zonisamide on human carbonic anhydrase *in vitro*. Arznei-forschung 1993;43:416–418.

15. De Simone G, Di Fiore A, Menchise V, et al. Carbonic anhydrase inhibitors. Zonisamide is an effective inhibitor of the cytosolic isozyme II and mitochondrial isozyme V: Solution and X-ray crystallographic studies. Bioorg Med Chem Lett 2005;9:2315–2320.

16. Ghaemi SN, Zablotsku B, Filkowski MM, et al. An open prospective study of zonisamide in acute bipolar depression. J Clin Psychopharmacol 2006;26:385–388.

17. Drake ME, Greathouse NI, Renner JB, et al. Open-label zonisamide for refractory migraine. Clin Neuropharmacol 2004;27:278–280.

18. Information for Healthcare Professionals: Zonisamide (marketed as Zonegran, and generics). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm106934.htm. (Accessed August 31, 2011).

19. Inoue T, Kira R, Kaku Y, et al. Renal tubular acidosis associated with zonisamide therapy. Epilepsia 2000;41:1642–1644.

20. Henry RP. Multiple roles of carbonic anhydrase in cellular transport and metabolism. Annu Rev Physiol 1996;52:523–538.

21. Stinebaugh BJ, Schloeder FX, Tam SC, et al. Pathogenesis of distal renal tubular acidosis. Kidney Int 1981;19:1–7.

22. Karet FE, Gainza FJ, Gyory AZ, et al. Mutations in the chloride-bicarbonate exchanger gene AE1 cause autosomal dominant but not autosomal recessive distal renal tubular acidosis. Proc Nat Acad Sci 1998;98:6337–6342.

23. Miyamoto T, Kohsaka M, Koyama T. Psychotic episodes during zonisamide treatment. Seizure 2000;9:65–70.

24. Dewey CW, Guiliano R, Booth DM, et al. Zonisamide therapy for refractory idiopathic epilepsy in dogs. J Am Anim Hosp Assoc 2004;40:285–291.

25. Booth DM, Perkins J. Disposition and safety of zonisamide after intravenous and oral single dose and oral multiple dosing in normal hound dogs. J Vet Pharmacol Ther 2008;31:544–553.